PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 0146-2026 WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/23985	International filing date *(day/month/year)* 31 August 2000 (31.08.2000)	Priority date *(day/month/year)* 31 August 1999 (31.08.1999)
International Patent Classification (IPC) or national classification and IPC IPC(7): G01N 33/566; C07K 14/705; C07J 1/00, 3/00 and US Cl.: 435/7.1, 7.2; 530/350; 514/169		
Applicant TRUSTEES OF BOSTON UNIVERSITY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26 March 2001 (26.03.2001)	11 December 2001 (11.12.2001)
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Claire M. Kaufman Telephone No. (703)308-0196

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/23985

I. Basis of the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-76 as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☒ the claims:
pages 77-85 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☒ the drawings:
pages 1-32 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listi has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 9,10,18,19,22-24 and 34-57

because:

☐ the said international application, or the said claim Nos. ____ relate to the following subject matter which doe not require international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. ____ are so uncle that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. ____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 9,10,18,19,22-24 and 34-57

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

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V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	3-8, 11, 13-17, 21, 25, 30, 32	YES
	Claims	1, 2, 12, 20, 26-29, 31, 33	NO
Inventive Step (IS)	Claims	7, 15, 16, 21, 25	YES
	Claims	1-6, 8, 11-14, 17, 20, 26-33	NO
Industrial Applicability (IA)	Claims	1-8, 11-17, 20-21, 25-33	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

Please See Continuation Sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claim 1 is objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claim is indefinite for the following reason(s): It is unclear in part c) if the measurement is relative to the receptor activity in the presence of the neurotransmitter recognition site ligand. That is, if the activity is increased by the ligand in the absence of the candidate modulator but the modulator causes a further increase, is that included in the claim. As the claim is written it is unclear if all members of the plurality of NMDA receptors have a increase in the presence of the ligand but only some have an increase in the presence of the candidate modulator, then that assay may be considered as reading on the claim.

Claims 7, 15 and 21 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claims are indefinite for the following reason(s): It is unclear if the chimera is limited to combinations of NR subunits are include chimeras consisting of one subunit and, for example, a purification tag or IgG domain.

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Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Claims 1, 2, 26-28, 31 and 33 lack novelty under PCT Article 33(2) as being anticipated by NAKANISHI ET AL.
NAKANISHI ET AL. teach a method of identifying a subunit specific modulator of NMDA receptor by contacting a NMDA receptor comprising NR1A or NR2B with NMDA, a neurotransmitter recognition site ligand, in the presence and absence of a modulator, D-APV; and, assaying for receptor activity by observing an increase in the presence but not the absence of the modulator (page 8554, FIG. 3) relative to the activity of the receptor in the presence of the neurotransmitter.

Claims 1, 2, 12, 20, 27-29, 31 and 33 lack novelty under PCT Article 33(2) as being anticipated by LAURI ET AL.
LAURI ET AL. teach a method of identifying a subunit specific modulator of NMDA receptor by contacting a NMDA receptor comprising NR1 and NR2A, -B, -C or -D with glutamate, a neurotransmitter recognition site ligand, in the presence and absence of a modulator, CGP 39653; and, assaying for receptor activity by observing a decrease in the presence but not the absence of the modulator (Table 2) relative to the activity of the receptor in the presence of the neurotransmitter. The findings showed (page 338, column 2, first full paragraph) that "No significant binding of [^{3}H] CGP 39653 to other homo- or heteromeric receptors [beside NR1-NR2A] could be detected by filtration or centrifugation binding assay". This method also used antagonists such as 5, 7-dichlorokynurenate (page 338, column 2, first and second full paragraphs).

Claims 1-6, 8, 11-14, 17, 20-21 and 26-33 lack an inventive step under PCT Article 33(3) as being obvious over LAURI ET AL. and NAKANISHI ET AL. as relied upon above in view of PARK-CHUNG ET AL.
The teachings of LAURI ET AL. and NAKANISHI ET AL. are relied upon set forth above.
PARK-CHUNG ET AL. teach a method of identifying a subunit specific modulator of NMDA receptor by contacting a NMDA receptor comprising NR1$_{100}$ and NR2A with, NMDA, a neurotransmitter recognition site ligand, in the presence and absence of a modulator, pregnenolone sulfate or 3ß5ßS; and, assaying for receptor activity by observing an increase or decrease in the presence but not the absence of the modulator (page 1119, column 1, section beginning "PS and 3ß5ßS act through....").
It would have been obvious to one of ordinary skill in the art to practice the method of claim 1 wherein either the NR1 submit was the same and NR2 subunit differed or vice versa sine both LAURI et al. and NAKANISHI ET AL. showed that the assay works either way. Note that NR1B has an alpha exon. It further would have been obvious to use as the candidate modulator a steroid or non-steroid based molecule as demonstrated by the above references, since both kinds were known to bind to and activate NMDA receptors. It further would have been obvious to use as the modulator a molecule from a library of small molecules because the methods of making and using such libraries was old and well known in the art and their use was routine for receptor screening to identify ligands.

Claims 7, 15, 16, 21 and 25 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest using a chimeric NR1 or NR2 subunit, wherein the chimera comprises at least one part of each of two distinct NR subunits, or using

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

subunits with point mutations because while the prior art does have limited teachings of chimeras and point mutants, their use would not be obvious in the instant method because there is no suggestion for their use in the identification of subunit specific modulators in the prior art.

Claims 1-8, 11-17, 20-21 and 25-33 meet the criteria set out in PCT Article 33(4), because they have industrial applicability.

---------- NEW CITATIONS ----------

NAKANISHI ET AL. Alternative splicing generates functionally distinct N-methyl-D-aspartate receptors. Proc. Natl. Acad. Sci. USA. September 1992, Vol. 89, pages 8552-8556, especially Figure 3.